

Linaclootide (Linzess) for Irritable Bowel Syndrome With Constipation and For Chronic Idiopathic Constipation

Rachel Hutchins Thomas, PharmD, MS; and Kyle Allmond



INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional disorder of the gastrointestinal (GI) tract, characterized by abdominal pain and altered bowel functioning that result in physical, psychological, social, and economic detriment to patients. IBS encompasses three subtypes differentiated by the predominant bowel habit: IBS with predominant diarrhea (IBS-D), IBS with predominant constipation (IBS-C), and IBS with mixed bowel habits (IBS-M).

The symptoms characteristic of IBS are typically relapsing or remitting in nature and cannot be explained by structural or biochemical abnormalities in the GI tract.^{1,2} IBS is the most commonly diagnosed GI disorder, with an estimated prevalence rate of 7% in North America.³ It is more common in females and in lower socioeconomic groups.³ The diagnosis declines with age (with most affected individuals younger than age 50), and it is symptom-based. A definitive diagnosis is often difficult, because symptoms supporting the diagnosis of IBS are nonspecific (e.g., abdominal pain; bloating; or abnormal stool frequency, form, or passage).

Several diagnostic tools for IBS have been developed (e.g., the Rome criteria and the Manning criteria). The American

College of Gastroenterology has also created a simplified algorithm for clinical use that defines IBS as abdominal pain accompanied by altered bowel habits persisting for at least 3 months.³

In patients with chronic idiopathic constipation (CIC), abdominal pain is minimal.⁴ Although many patients with CIC experience some degree of abdominal pain or discomfort, pain is a secondary concern. The estimated prevalence of CIC in North America is 14%, with higher rates in women and the elderly.⁵

Treatment options for IBS-C and CIC are limited. Nonpharmacological measures (i.e., diet and lifestyle modifications) are recommended, and over-the-counter drugs are used, but they are not approved by the FDA for this indication. Bulk-forming, osmotic, and stimulant laxatives, for example, may alleviate constipation, but they do not treat abdominal pain or discomfort. Furthermore, their effectiveness in the management of IBS-C and CIC has not been established.³

Three medications, one of which was removed from the market, are approved by the FDA for treating IBS-C and CIC.

Lubiprostone (Amitiza, Takeda), a prostaglandin analogue and a locally acting selective CIC-2 chloride channel activator, was approved in 2008 for the treatment of IBS-C in women 18 years of age and older and for the treatment of CIC in adults.^{6,7} Adverse effects associated with lubiprostone include dose-related nausea and dyspnea with chest tightness.⁶⁻¹⁰

Tegaserod (Zelnorm, Novartis), a serotonin-4 agonist, was approved in 2002 for the short-term treatment of IBS-C in women and in 2004 for the treatment of CIC in adults 65 years of age or younger.¹¹ In early 2007, the FDA restricted the use of tegaserod under an Investigational New Drug protocol because of postmarketing reports of serious cardiovascular adverse effects. The manufacturer has subsequently limited the use of tegaserod in emergency situations only.¹²⁻¹⁴

In August 2012, linaclootide (Linzess, Ironwood/Forest) was approved for the treatment of IBS-C and CIC in adults. This represents the second FDA-approved pharmacological treatment option on the market for these chronic GI tract disorders.¹⁵

MECHANISM OF ACTION

Linaclootide is a first-in-class, 14-amino acid peptide of the guanylin peptide family and acts as a selective agonist at the guanylate cyclase-C (GC-C) receptor on the luminal surface of intestinal enterocytes. The endogenous ligands of GC-C (guanylin peptide hormones guanylin and uroguanylin) bind to the receptor to promote intestinal secretions in response to a meal. Activation of GC-C by guanylin peptides, including linaclootide, results in increased levels of cyclic guanosine monophosphate (cGMP), a second messenger that plays a critical role in the regulation and secretion of intestinal fluid.¹⁶⁻¹⁹

Elevation of intracellular cGMP triggers the activation of cGMP protein kinase and subsequent phosphorylation of downstream targets, including the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel. Activation of the CFTR channel results in increased secretion of chloride and bicarbonate ions into the intestinal lumen, culminating in increased intestinal fluid secretion and accelerated GI transit.

In rodent models of visceral hypersensitivity, linaclootide reduced intestinal pain, probably a result of a desensitization of afferent pain fibers mediated by activation of GC-C.^{20,21} Therefore, GC-C is emerging as a therapeutic target for the treatment of IBS-C and CIC as a result of its dual role in accelerating GI transit and decreasing abdominal pain.

PHARMACOKINETICS AND PHARMACODYNAMICS

Linaclootide elicits its pharmacological effects locally in the GI tract with mini-

Dr. Thomas is Assistant Professor of Pharmacy Practice and Drug Information Specialist at Samford University Global Drug Information Service, McWhorter School of Pharmacy, in Birmingham, Alabama. Mr. Allmond is a pharmacy doctoral student at the school. Drug Forecast is a regular column coordinated by Alan Caspi, PhD, PharmD, MBA, President of Caspi & Associates in New York, New York.

Disclosure. The authors report that they have no commercial or financial relationships in regard to this article. This work was self-funded, and the authors have no conflicts of interest to declare.

mal systemic absorption following oral administration. It is resistant to degradation by stomach acid and trypsin, pepsin, aminopeptidase, and chymotrypsin; however, it produces a single 13-amino acid degradation product when exposed to carboxypeptidase.²² Both linaclotide and its metabolite are activated by oxidation in the GI tract. In the intestinal lumen, linaclotide is deactivated by reduction of its disulfide bonds and is further degraded into smaller peptides and amino acids; 3% to 5% of the intact active drug or metabolite is excreted in the feces.^{21,22}

In studies of rodents, the oral bioavailability of linaclotide and its metabolite was 0.1% or less following a single 10-mg/kg dose.^{18,22} and the parent drug was completely degraded to its metabolite within 30 minutes with a first-order half-life of only 3 minutes.²³

Three phase 1 clinical trials and a random sampling in four phase 3 trials confirmed minimal systemic exposure to linaclotide in humans; plasma concentrations were less than 1 ng/mL and were often below measurable levels.²² Pharmacokinetic parameters of oral linaclotide, including area-under-the-curve (AUC) concentrations, maximum concentrations (C_{max}), and elimination half-life, cannot be calculated because of the lack of systemic absorption of the drug and its metabolite.²¹ GI transit times in rodents suggest that pharmacologically active concentrations of linaclotide are present in the colon 1 hour following oral administration.²⁰

Both linaclotide and its active metabolite bind to GC-C with similar affinities in a pH-independent manner and result in dose-dependent increases in intracellular cGMP production, as shown by *in vitro* and *in vivo* rodent studies. The concentration of linaclotide required to produce 50% of maximal activity (EC_{50}) is eight-fold to ten-fold greater than that of guanylin or uroguanylin at pH 7.¹⁸ Increases in intracellular cGMP and the accompanying increases in intestinal fluid secretion are more pronounced in the duodenum and jejunum than in the ileum. The resulting increases in intestinal transit speed were shown to be dose-dependent in both male and female rodent models.²²

In clinical trials of linaclotide, dose-dependent improvements in stool frequency were noted.^{21,24,25} Improved stool consistency was also observed, as measured by the Bristol Stool Form Scale

(BSFS), a 7-point scale ranging from 1 (separate hard, difficult-to-pass lumps) to 7 (liquid stools). A score of less than 3 is considered constipation.^{1,26} Alleviation of abdominal pain and discomfort was demonstrated in rodent models and confirmed in clinical trials.^{20,27–29}

Renal or hepatic impairment is thought to be irrelevant in the metabolism of linaclotide because of the drug's lack of systemic absorption.²¹ Food effects were studied in a phase 1 crossover study in fasted or fed subjects who received linaclotide 290 mcg daily for 7 days. Linaclotide was not systemically absorbed regardless of food intake.²² Subjects who were given a single dose of 2,897 mcg (10 times the therapeutic dose) also had no measurable linaclotide plasma levels, except for two of the nine fasted subjects (C_{max} , 0.735 ng/mL and 0.212 ng/mL).²² Compared with the fasted state, the administration of linaclotide immediately following a high-fat breakfast resulted in looser stools and a higher stool frequency.²¹ In all clinical trials, linaclotide was given 30 minutes before breakfast.^{27–29}

PIVOTAL CLINICAL TRIALS

In 2010, the FDA recommended that all drugs being considered for approval in IBS meet a symptoms-based co-primary endpoint that includes both improved abdominal pain intensity (a reduction of 30% or more from baseline in average daily worst pain score) and stool frequency (an increase of one or more complete spontaneous bowel movements [CSBMs] per week from baseline) for at least half of the study's duration.³⁰

The approval of linaclotide was based on two phase 3 trials of IBS-C that included the FDA-recommended dual primary endpoint and two phase 3 trials of CIC that measured a primary endpoint that the FDA considered to be rigorous.³¹ Patients were eligible for enrollment in phase 3 trials if they met the criteria presented in Table 1. Inclusion criteria for IBS-C studies were based on the modified Rome II criteria, which have since been updated to Rome III; however, Rome II was used in preliminary studies of linaclotide and was continued throughout the trials for consistency.

Irritable Bowel Syndrome With Constipation

Study designs, endpoints, and patient

demographics were similar in the two phase 3 trials.^{27,28} Most patients in both trials were female (90%–91%) and Caucasian (77%–78%). The active-treatment period of each trial was preceded by a 2-week screening phase in which baseline bowel symptoms were recorded.

Most patients (87%–88%) reported baseline daily abdominal pain (mean scores, 5.6–5.7 and 5.5–5.6 for linaclotide and placebo, respectively). An 11-point scale ranging from 0 to 10 (0 = no pain, 10 = severe pain) was used. Seventy-six percent of patients reported an absence of CSBMs, defined as spontaneous bowel movements accompanied by a feeling of complete evacuation, at baseline, with a mean of 0.2 CSBMs/week for each group in both studies.

Patients were permitted to continue any stable baseline regimens of fiber, stool softeners, bulk laxatives, or probiotics throughout the trials. The primary efficacy endpoints were designed to meet the FDA recommendations for IBS drug approval (i.e., an improvement of 30% or more in daily worst abdominal pain scores and an increase of one or more CSBMs/week from baseline for at least 6 of the 12 weeks of treatment).

A more rigorous primary endpoint was established that required patients to meet the following criteria for 9 of 12 weeks: an improvement of 30% or greater in daily worst abdominal pain scores and three or more CSBMs/week with an increase of one or more CSBMs/week from baseline. Secondary endpoints included the following:^{27,28}

- abdominal pain, bloating, and discomfort, as measured by 11-point numerical scales
- severity of straining and constipation, as assessed by 5-point ordinal scales
- weekly stool frequency, as measured by CSBMs
- spontaneous bowel movements (SBMs), defined as occurring without use of laxatives, enemas, or suppositories within the preceding 24 hours
- stool consistency, as measured by BSFS scores

Key efficacy findings of the two phase 3 clinical trials in IBS-C are presented in Table 2.

Phase 3, Study 1

In a double-blind, randomized, placebo-controlled trial, patients with IBS-C (n = 804) received linaclotide 290 mcg or placebo daily for 26 weeks. Change-from-baseline endpoints were analyzed over the first 12 weeks and for the entire 26-week trial.

Over the initial 12-week period, both components of the FDA co-primary endpoint were achieved by 33.7% of patients receiving linaclotide compared with 13.9% of patients receiving placebo ($P < 0.0001$). The number of patients needed to treat (NNT) was 5.1, and the 95% confidence interval (CI) was 3.9 to 7.1.

The pain-response component of the FDA endpoint was met by 48.9% of the linaclotide patients and by 34.5% of the placebo patients ($P < 0.0001$; NNT, 7.0; 95% CI, 4.7–13.1), whereas the stool frequency component was met by 47.6% of patients receiving linaclotide and by 22.6% of patients receiving placebo ($P < 0.0001$; NNT, 4.0; 95% CI, 3.2–5.4).

The more rigorous primary endpoint (an improvement of 30% or more in daily worst abdominal pain scores and three or more CSBMs/week with an increase of one or more CSBMs/week from baseline for 9 of 12 weeks) was achieved in 12.7% of linaclotide patients and in 3.0% of placebo patients ($P < 0.0001$; NNT, 10.3; 95% CI, 7.5–16.4). Positive outcomes were also demonstrated in the linaclotide group over a period of 26 weeks; the FDA's co-primary endpoint was achieved by 32.4% of patients receiving linaclotide and by 13.2% of patients receiving placebo ($P < 0.0001$) for at least 13 of the 26 weeks (NNT, 5.2; 95% CI, 4.0–7.3).

Table 1 Criteria for Enrollment in Phase 3 Clinical Trials of Linaclotide

Irritable bowel syndrome with constipation	<p>Abdominal pain or discomfort for at least 12 weeks in the 12 months prior to study enrollment that was characterized by at least two of the following:</p> <ul style="list-style-type: none"> relief upon defecation onset associated with a change in frequency of stool onset associated with a change in form of stool <p>and</p> <p>At least one of the following symptoms during more than 25% of bowel movements:</p> <ul style="list-style-type: none"> straining lumpy or hard stools sensation of incomplete evacuation <p>Additional criteria that had to be met during the 2-week screening phase:</p> <ul style="list-style-type: none"> an average score above 3 for worst daily abdominal pain (on a scale of 0 to 10) an average of five or fewer SBMs/week an average of fewer than three CSBMs/week
Chronic idiopathic constipation	<p>An average of fewer than three SBMs/week</p> <p>and</p> <p>At least one of the following symptoms during more than 25% of bowel movements:</p> <ul style="list-style-type: none"> straining lumpy or hard stools sensation of incomplete evacuation <p>Additional criteria that had to be met during the 2-week screening phase:</p> <ul style="list-style-type: none"> an average of six or fewer SBMs/week an average of fewer than three CSBMs/week

SBMs = spontaneous bowel movements; CSBMs = complete SBMs.

In all secondary endpoints at weeks 12 and 26, linaclotide demonstrated small but statistically significant improvements. Patients reported less abdominal pain, discomfort, and bloating with reductions of approximately 1.9 and 2.1 points (on an 11-point scale) from baseline at weeks 12 and 26, respectively, compared with re-

ductions of 1.1 and 1.2 points with placebo ($P < 0.001$ vs. placebo for each measure).

Severity of straining and of constipation was also reduced with linaclotide at weeks 12 and 26 by a mean of approximately 1.2 points (on a 5-point scale) compared with 0.7 points with placebo ($P < 0.0001$). Linaclotide-treated patients

Table 2 Key 12-Week Efficacy Results in Phase 3 Clinical Trials of Linaclotide 290 mcg in Irritable Bowel Syndrome With Constipation

Trial (n)	FDA Co-primary Endpoint*			Pain Component of FDA Co-primary Endpoint			Stool Frequency Component of FDA Co-primary Endpoint			Other Primary Endpoint†		
	LIN	PBO	NNT	LIN	PBO	NNT	LIN	PBO	NNT	LIN	PBO	NNT
Chey et al. (n = 804) ²⁷	33.7%	13.9%	5.1	48.9%	34.5%	7.0	47.6%	22.6%	4.0	12.7%	3.0%	10.3
Rao et al. (n = 800) ²⁸	33.6%	21%	8.0	50.1%	37.5%	7.9	48.6%	29.6%	5.3	12.1%	5.1%	14.2

LIN = linaclotide 290 mcg; NNT = number needed to treat; PBO = placebo.

*Improvement in both pain (a reduction of 30% or more from baseline in average daily worst pain score) and stool frequency (an increase of one or more complete spontaneous bowel movements/week from baseline) for 6 of 12 weeks.

†A 30% reduction or more from baseline in average daily worst pain score, three or more complete spontaneous bowel movements/week, and an increase of one or more complete spontaneous bowel movements/week from baseline for 9 of 12 weeks.

reported a mean increase from baseline of 2.2 CSBMs/week at weeks 12 and 26, compared with 0.7 CSBMs/week for placebo patients ($P < 0.0001$); 28.9% of treated patients had a CSBM within 24 hours of the first dose, compared with 8.4% receiving placebo ($P < 0.0001$).

Despite these statistically significant increases in mean CSBMs, baseline values were low (about 0.2 per week), and the mean CSBM rate following linaclotide treatment continued to meet the entry criteria for constipation (fewer than three CSBMs/week). Stool consistency, as assessed by BSFS scores, was also improved at weeks 12 and 26 with linaclotide compared with placebo. The change from baseline was 1.9 and 0.6 points, respectively, at both weeks 12 and 26 ($P < 0.0001$). This change in BSFS score represents an improvement from a score of 2 (constipation; sausage-shaped but lumpy stools) at baseline in each group to a score of 4 (smooth and soft) with linaclotide, and a score of 3 (cracked surface) with placebo.²⁷

Treatment-related adverse effects were generally mild to moderate in severity; diarrhea was the only adverse effect that occurred at a significantly greater incidence with linaclotide than with placebo (19.7% vs. 2.5%, respectively; $P < 0.0001$). Diarrhea occurred most often within the first 4 weeks of linaclotide therapy and was categorized as severe by 2.0% of linaclotide patients.

Discontinuation rates were 10.2% and 2.5% for linaclotide and placebo, respectively. No clinically significant changes in vital signs were noted. For five patients receiving linaclotide, serum bicarbonate levels were below the lower limit of normal; one of these patients had reported diarrhea as an adverse effect.²⁷

Phase 3, Study 2

The second randomized phase 3 trial of IBS-C included a 12-week active-treatment period, followed by a 4-week withdrawal period in which the effects of linaclotide discontinuation were measured. Patients with IBS-C ($n = 800$) received either linaclotide 290 mcg once daily or placebo for 12 weeks. After completing the double-blind treatment period, members of the initial linaclotide group were re-randomized to receive either linaclotide 290 mcg or placebo. Patients in the initial placebo group were assigned to

linaclotide during the withdrawal phase. A total of 647 patients (81%) in the 12-week treatment phase entered the 4-week withdrawal phase.

Compared with placebo, linaclotide demonstrated statistically significant improvements in all primary and secondary efficacy endpoints. Over the 12-week treatment period, 33.6% of linaclotide patients met both components of the FDA endpoint compared with 21% of placebo patients ($P < 0.0001$; NNT, 8.0; 95% CI, 5.4–15.5).

The pain-response component was achieved by 50.1% of patients receiving linaclotide and by 37.5% receiving placebo ($P = 0.0003$; NNT, 7.9; 95% CI, 5.1–17.1). Improvements in pain were noted during the first week of therapy. Maximum improvements were achieved after 6 to 8 weeks and were sustained throughout the treatment period.

The stool-frequency component of the FDA endpoint was met by 48.6% of the linaclotide group and by 29.6% of placebo patients ($P < 0.0001$; NNT, 5.3; 95% CI, 3.9–8.1). Linaclotide was also superior to placebo in the percentage of patients who met the more rigorous primary endpoint, which required even more CSBM responses for 9 of 12 weeks (linaclotide, 12.1%; placebo, 5.1%) ($P = 0.0004$; NNT, 14.2; 95% CI, 9.2–31.3).

Small but statistically significant improvements in abdominal pain, discomfort, and bloating were noted in the linaclotide-treated patients, with a mean change from baseline of approximately –2 points (on an 11-point scale), compared with –1.1 with placebo ($P < 0.001$ for each measure). Severity of straining was also reduced with linaclotide (change from baseline, –1.3 points on a 5-point scale vs. –0.7 with placebo; $P < 0.0001$), as was severity of constipation (change from baseline, –1.2 points on a 5-point scale vs. –0.6 with placebo; $P < 0.0001$).

Patients receiving linaclotide reported a mean increase from baseline of 2.3 CSBMs/week, compared with 0.7 CSBMs/week for placebo ($P < 0.0001$); 32.3% of patients experienced a CSBM within 24 hours of the first dose, compared with 13.2% of placebo patients ($P < 0.0001$). Increases in CSBMs differed significantly between linaclotide and placebo; however, as was also seen in the first phase 3 trial,²⁷ linaclotide did not result in increased CSBM rates to exceed

the Rome II criteria cutoff for constipation (fewer than three CSBMs/week).

Improvements in stool consistency, as measured by BSFS scores, were also significantly greater for linaclotide than for placebo. Scores at baseline were 2.3 and 2.4, respectively; scores after 12 weeks of treatment were 4.5 and 3.1, respectively ($P < 0.0001$).²⁸

In response to linaclotide withdrawal, abdominal pain recurred and CSBMs decreased to levels similar to those observed in the placebo group in the initial 12-week treatment period. In contrast, patients in the initial linaclotide group who continued to receive active treatment throughout the 4-week withdrawal phase exhibited statistically significant sustained improvements, compared with placebo, in weeks 13 to 16 for stool frequency ($P < 0.001$) and in weeks 14 to 16 for abdominal pain ($P < 0.05$).

Patients initially receiving placebo who were assigned to linaclotide during the 4-week withdrawal phase experienced reductions in pain and stool frequency, similar to those reductions observed with linaclotide patients during the 12-week treatment phase. No evidence of rebound (i.e., worsening of IBS-C symptoms after stopping linaclotide) was apparent.²⁸

Treatment-emergent adverse events were mild or moderate in severity, with linaclotide patients reporting significantly higher rates of diarrhea ($P < 0.0001$), flatulence ($P = 0.0084$), and abdominal pain ($P = 0.0462$) compared with placebo patients. Reports of diarrhea, experienced by 19.5% of linaclotide-treated patients and by 3.5% of placebo-treated patients, were not accompanied by clinically significant sequelae.

Decreases in serum bicarbonate to below the lower limit of normal were reported in seven patients receiving linaclotide and in one patient receiving placebo, but none of these patients reported diarrhea. Treatment was discontinued by 7.9% of linaclotide patients and by 2.8% of placebo patients because of adverse events, mainly diarrhea.²⁸

Chronic Idiopathic Constipation

Trials 303 and 01

The FDA's approval of linaclotide for the treatment of CIC was based on data from two randomized, double-blind, placebo-controlled, 12-week phase 3 trials (303 and 01), which investigated

the efficacy and safety of 145-mcg and 290-mcg doses ($n = 1,272$). These trials (Nos. NCT00765882 and NCT00730015) were similar in their study design and endpoints, and patient demographics were comparable.

Trial 303 also included a 4-week withdrawal phase in which linaclotide patients who completed the 12-week treatment phase were re-randomized to either placebo or linaclotide. All patients receiving placebo during the treatment phase were assigned to receive linaclotide 290 mcg during the withdrawal phase.

The primary endpoint of each trial was the proportion of patients who achieved three or more CSBMs/week and an increase in one or more CSBMs/week above baseline for at least 9 of 12 weeks. Secondary endpoints included:

- stool frequency, as measured by weekly CSBM and SBM rates
- stool consistency, as assessed by BSFS scores
- severity of straining, abdominal discomfort, bloating, and constipation, as measured by 5-point ordinal scales

Most patients in both trials were women (87%–92%) and Caucasian (73%–79%). Key efficacy findings of the two phase 3 clinical trials in CIC are presented in Table 3.

In both trials, significantly more patients receiving linaclotide achieved the primary endpoint compared with those receiving placebo. The primary endpoint was met by 21.2% and 16.0% of patients in the 145-mcg groups and by 19.4% and 21.3% of patients in the 290-mcg groups, compared with 3.3% and 6.0% of patients in the placebo groups ($P < 0.01$ for each linaclotide dose vs. placebo for each trial). However, differences in response rates between the two linaclotide doses were not significant ($P = 0.63$, Trial 303; $P = 0.19$, Trial 01). This apparent lack of a dose–response effect led to the FDA's approval of the 145-mcg dose for patients with CIC.²⁹

Increases in weekly CSBM rates in linaclotide-treated patients were evident at week 1 and were sustained throughout the 12-week trials. In both trials, linaclotide-treated patients reported a mean increase from baseline of 2.0 CSBMs/week with 145 mcg and 2.0 to 2.7 CSBMs with 290 mcg, compared with

0.5 CSBMs with placebo ($P < 0.001$).

From 28.2 to 33.2% of patients receiving 145 mcg and from 26.9 to 29.7% of patients receiving 290 mcg experienced a CSBM within 24 hours of the first dose, compared with 11.0% to 13.5% of those receiving placebo ($P < 0.001$). Similar to results seen in the IBS–C trials, after 12 weeks of therapy, the linaclotide patients (with a mean baseline CSBM/week of 0.3) experienced statistically significant increases in CSBM rates but continued to have a mean of fewer than three CSBMs/week, thus meeting the criteria for constipation.

During the 4-week withdrawal phase in Trial 303, patients who stayed with linaclotide therapy sustained improved CSBM rates, whereas patients who initially received placebo and then were switched to linaclotide 290 mcg reported increases in CSBM rates similar to those seen in the 12-week treatment phase. In patients who were switched from linaclotide to placebo, CSBM rates declined to rates similar to those for placebo during the 12-week treatment phase, but there was no apparent evidence of rebound (i.e., worsening of CIC symptoms after discontinuation of linaclotide).²⁹

Compared with placebo, linaclotide also resulted in statistically significant improvements from baseline in all secondary efficacy measures in patients with CIC. Stool consistency, as measured by BSFS scores, improved from approximately 2 at baseline (hard or lumpy stools) to approximately 4 after treatment (softer stools), compared with a score of 3 for placebo ($P < 0.001$).

Changes from baseline scores in abdominal discomfort (range of means for linaclotide, -0.5 to -0.4 vs. -0.3 in placebo groups), straining severity (-1.1 to -1.2

vs. -0.5), bloating (-0.4 to -0.5 vs. -0.2), and constipation severity (-0.81 to -0.95 vs. -0.27 to -0.31) were all statistically significant when compared with placebo ($P < 0.05$).²⁹ However, the small improvements in these ordinal scale measurements (on a 5-point scale) make it difficult to assess clinical meaningfulness.

Diarrhea was the most frequently reported adverse event, affecting 16.0% of patients treated with 145 mcg, 14.2% of those who received 290 mcg, and 4.7% of those receiving placebo. The first incidence of diarrhea was reported most often during the first 2 weeks of therapy. Severe diarrhea affected 1.5% of patients who received linaclotide, compared with 0.2% of patients who received placebo.

Discontinuation rates, which were most commonly attributed to diarrhea, were 7.9% with linaclotide 145 mcg, 7.3% with 290 mcg, and 4.2% with placebo. No clinically significant differences in laboratory values or vital signs were noted between the linaclotide and placebo groups.²⁹

SAFETY

As expected, because of linaclotide's mechanism of action as a secretagogue, diarrhea is the most frequently reported adverse event associated with the drug. Rates of diarrhea in the four phase 3 clinical trials were 16.0% with 145 mcg in patients with CIC and 14.2% to 19.7% with 290 mcg in patients with CIC or IBS–C. Severe diarrhea occurred in 0% to 2% of patients receiving linaclotide. Diarrhea was not associated with clinically relevant sequelae.

Most patients reported the first episode of diarrhea within the first 2 to 4 weeks of treatment.^{27–29} Other adverse events occurring more frequently with

Table 3 Key Efficacy Results in Phase 3 Clinical Trials of Linaclotide 145 mcg and 290 mcg in Chronic Idiopathic Constipation

Trial (n)	Primary Endpoint*			NNT	
	LIN 145 mcg	LIN 290 mcg	PBO	LIN 145 mcg	LIN 290 mcg
Trial 303 (n = 642)	21.2%	19.4% ^a	3.3%	5.6	6.2
Trial 01 (n = 630)	16.0%	21.3% ^b	6.0%	10.1	6.6

^a $P = 0.63$ for linaclotide 145 mcg vs. 290 mcg.

^b $P = 0.19$ for linaclotide 145 mcg vs. 290 mcg.

LIN = linaclotide; NNT = number needed to treat; PBO = placebo.

*Proportion of patients with both three or more complete spontaneous bowel movements (CSBMs)/week and an increase of one or more CSBMs/week from baseline for 9 of 12 weeks.

Data from Lembo AJ, et al. *N Engl J Med* 2011;365(6):527–536.

linaclotide than with placebo were abdominal pain (7% vs. 5%), flatulence (4% vs. 2%), headache (4% vs. 3%), viral gastroenteritis (3% vs. 1%), and abdominal distention (2% vs. 1%).²¹

Infrequent adverse events suggestive of hypersensitivity to linaclotide were observed in clinical trials, leading the FDA to suspect potential production of auto-antibodies against the peptide and to order postmarketing studies of immunogenicity of linaclotide.³¹

A boxed warning for linaclotide is included for use in pediatric patients 6 to 17 years of age because of deaths associated with single adult doses in juvenile mice. Linaclotide is contraindicated in patients 6 years of age and younger and in patients with mechanical obstruction of the GI tract.²¹

Linaclotide is a Pregnancy Category C drug. Animal studies showed fetal toxicity only at doses that were toxic to the mother, but trials in pregnant women have not been conducted. Linaclotide is not expected to enter breast milk because of its minimal systemic absorption, although the safety of linaclotide in breast-feeding mothers has not been evaluated in clinical trials. As a condition of approval, the FDA required postmarketing studies in this area.³¹

DOSAGE AND ADMINISTRATION

The approved dose of linaclotide is one 290-mcg capsule once daily in adults with IBS-C and one 145-mcg capsule once daily in adults with CIC. Linaclotide should be taken in the morning 30 minutes before breakfast. Although linaclotide has not been studied in patients with renal or hepatic renal impairment, these conditions are unlikely to affect the metabolism or clearance of the parent drug or metabolite because of the low systemic availability following oral administration. No dosage adjustments are needed.²¹

P&T COMMITTEE CONSIDERATIONS

The approval of linaclotide for the treatment of IBS-C and CIC marks the entry of another drug into the market for which only one other prescription drug therapy currently exists: Takeda's lubiprostone (Amitiza). Compared with the twice-daily regimen of lubiprostone, linaclotide offers the convenience of once-daily dosing; it is also the only agent approved for the treatment of IBS-C in both men

and women 18 years of age and older. Lubiprostone, however, is approved for IBS-C only for women 18 years of age and older. Both drugs have minimal systemic absorption and minimal drug-drug interactions.

Dosage adjustments are initially required for lubiprostone in patients with severe hepatic impairment. No dosage adjustments are needed for linaclotide patients with renal or hepatic impairment.

Although diarrhea was reported in clinical trials with both linaclotide (in 14%–20% of patients) and lubiprostone (in 12%), lubiprostone has also been associated with dyspnea, chest discomfort, and edema. Nausea is also frequent with lubiprostone, occurring in 8% and 29% of patients receiving 8 mcg (for IBS-C) and 24 mcg (for CIC) twice daily, respectively, but these events are rare with linaclotide.^{6,7,21}

The long-term safety and efficacy of linaclotide have not been evaluated beyond 26 weeks, and comparative effectiveness studies have not been conducted to directly compare it with lubiprostone. Postmarketing surveillance studies will be beneficial in uncovering any rare adverse events associated with linaclotide.

COST

Linaclotide is available as 145-mcg and 290-mcg capsules. The average wholesale price (AWP) is \$255 for 30 capsules.³² This pricing is comparable to that of lubiprostone (AWP, \$296 for a 1-month supply of 8-mcg or 24-mcg capsules).³³ The cost of both agents may limit their formulary availability to patients who are not successfully treated by nonpharmacological measures and over-the-counter agents.

CONCLUSION

Linaclotide is an efficacious, well-tolerated treatment option for adults with irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC). This medication improves both bowel symptoms and abdominal pain and discomfort. Both phase 3 clinical trials of linaclotide 290 mcg in IBS-C met the FDA-mandated co-primary IBS response endpoint in approximately one-third of patients, with the number needed to treat (NNT) ranging from five to eight patients.

In patients with CIC, both phase 3 trials of linaclotide 145 mcg and 290 mcg met

the primary endpoint in approximately 20% of patients, with the NNT ranging from six to 10 patients. Although the secondary endpoint of stool frequency (the rate of weekly CSBMs) was statistically significant in all phase 3 trials in IBS-C and CIC, the mean stool frequency after linaclotide treatment continued to meet the criteria for constipation (fewer than three CSBMs/week). However, the increase in frequency of CSBMs was considered clinically meaningful to patients, as they reported significant reductions in their perceived severity of constipation and relief of multiple symptoms, including abdominal discomfort and bloating.

Before the approval of linaclotide, patients with IBS-C and CIC had only one FDA-approved treatment option, lubiprostone (Amitiza). The approval of linaclotide marks an important expansion in the therapeutic options for IBS-C and CIC, especially for patients who have not tolerated or responded to lubiprostone. Further studies investigating long-term effectiveness and safety of linaclotide in larger populations are needed. Despite the cost of linaclotide, its efficacy and safety, in conjunction with the dearth of other treatments for IBS-C and CIC, make it an important emerging therapeutic option for patients with IBS-C or CIC.

REFERENCES

1. Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. *Gastroenterology* 2006;130(5):1480–1491; erratum, 2006;131(2):688.
2. Spiller R, Aziz Q, Creed F, et al. Clinical Services Committee of The British Society of Gastroenterology. Guidelines on the irritable bowel syndrome: Mechanisms and practical management. *Gut* 2007;56(12):1770–1798; erratum, 2008;57(12):1743.
3. Brandt LJ, Chey WD, Foxx-Orenstein AE, et al. American College of Gastroenterology Task Force on Irritable Bowel Syndrome: An evidence-based systematic review on the management of irritable bowel syndrome. *Am J Gastroenterol* 2009; 104:S1–S35.
4. Higgins PD, Johanson JF. Epidemiology of constipation in North America: A systematic review. *Am J Gastroenterol* 2004;99:750–751.
5. Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: Systematic review and meta-analysis. *Gut* 2011;60(2):209–218.
6. Amitiza (lubiprostone) capsules, prescribing information. Deerfield, Ill: Takeda; November 2012. Available at: <http://amitizahcp.com/default.aspx>. Accessed December 12, 2012.

7. Thomson Reuters Drugdex. Lubiprostone. Available at: www.thomsonhc.com. Accessed December 12, 2012.
8. Ambizas EM, Ginzburg R. Lubiprostone: A chloride channel activator for treatment of chronic constipation. *Ann Pharmacother* 2007;41(6):957-964.
9. Chamberlain SM, Rao SS. Safety evaluation of lubiprostone in the treatment of constipation and irritable bowel syndrome. *Exp Opin Drug Saf* 2012; 11(5):841-850.
10. Lembo AJ, Johanson JF, Parkman HP, et al. Long-term safety and effectiveness of lubiprostone, a chloride channel (ClC-2) activator, in patients with chronic idiopathic constipation. *Dig Dis Sci* 2011;56(9):2639-2645.
11. Elsevier Gold Standard Clinical Pharmacology Online. Tegaserod. Available at: <http://clinicalpharmacology.com>. Accessed December 12, 2012.
12. FDA announces discontinued marketing of GI drug, Zelnorm, for safety reasons. March 30, 2007. Available at: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108879.htm. Accessed September 19, 2012.
13. FDA permits restricted use of Zelnorm for qualifying patients. July 27, 2007. Available at: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108956.htm. Accessed September 19, 2012.
14. Zelnorm (tegaserod maleate) information. Available at: www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafety-InformationforPatientsandProviders/ucm103223.htm. Accessed September 19, 2012.
15. FDA approves Linzess to treat certain cases of irritable bowel syndrome and constipation, August 30, 2012. Available at: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm317505.htm#. Accessed September 20, 2012.
16. Schulz S, Green CK, Yuen PS, Garbers DL. Guanylyl cyclase is a heat-stable enterotoxin receptor. *Cell* 1990;63(5):941-948.
17. Bharucha AE, Linden DR. Linacotide: A secretagogue and antihyperalgesic agent. What next? *Neurogastroenterol Motil* 2010;22(3):227-231.
18. Busby RW, Bryant AP, Bartolini WP, et al. Linacotide, through activation of guanylate cyclase C, acts locally in the gastrointestinal tract to elicit enhanced intestinal secretion and transit. *Eur J Pharmacol* 2010;649(1-3):328-335.
19. Potter LR. Regulation and therapeutic targeting of peptide-activated receptor guanylyl cyclases. *Pharmacol Ther* 2011;130(1):71-82.
20. Eutamene H, Bradesi S, Larauche M, et al. Guanylate cyclase C-mediated antinociceptive effects of linacotide in rodent models of visceral pain. *Neurogastroenterol Motil* 2010;22(3):312-e84.
21. Linzess (linacotide) capsules, prescribing information. Cambridge, Mass.: Ironwood Pharmaceuticals; August 2012. Available at: www.frx.com/pi/linzess_pi.pdf. Accessed December 12, 2012.
22. Busby RW, Kessler MM, Bartolini WP, et al. Pharmacological properties, metabolism and disposition of linacotide, a novel therapeutic peptide approved for the treatment of irritable bowel syndrome with constipation and chronic idiopathic constipation. *J Pharmacol Exp Ther* 2013; 344(1):196-206.
23. Bryant AP, Busby RW, Bartolini WP, et al. Linacotide is a potent and selective guanylate cyclase C agonist that elicits pharmacological effects locally in the gastrointestinal tract. *Life Sci* 2010;86(19-20):760-765.
24. Kurtz C, Fitch D, Busby RW, et al. Effects of multidose administration of MD-1100 on safety, tolerability, exposure, and pharmacodynamics in healthy subjects (Abstract 132). *Gastroenterology* 2006;130:A26.
25. Currie MG, Kurtz C, Mahajan-Miklos S, et al. Effects of single dose administration of MD-1100 on safety, tolerability, exposure, and stool consistency in healthy subjects (Abstract 894). *Am J Gastroenterol* 2005;100:S328.
26. O'Donnell LJ, Virjee J, Heaton KW. Detection of pseudodiarrhoea by simple clinical assessment of intestinal transit rate. *BMJ* 1990;300(6722):439-440.
27. Chey WD, Lembo AJ, Lavins BJ, et al. Linacotide for irritable bowel syndrome with constipation: A 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol* 2012;107(11):1702-1712.
28. Rao S, Lembo AJ, Shiff SJ, et al. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linacotide in irritable bowel syndrome with constipation. *Am J Gastroenterol* 2012;107(11):1714-1724.
29. Lembo AJ, Schneier HA, Shiff SJ, et al. Two randomized trials of linacotide for chronic constipation. *N Engl J Med* 2011;365(6):527-536.
30. FDA, Center for Drug Evaluation and Research. *Guidance for Industry: Irritable Bowel Syndrome. Clinical Evaluation of Drugs for Treatment*. May 2012. Available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory-Information/Guidances/UCM205269.pdf. Accessed December 10, 2012.
31. FDA, Center for Drug Evaluation and Research. *Application No. 202811 OrigIs000. Summary Review*. August 29, 2012. Available at: www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202811Orig1s000SumR.pdf. Accessed December 10, 2012.
32. *Red Book Online*. Linacotide. Ann Arbor, Mich.: Truven Health Analytics. Available at: www.truvenhealth.com. Accessed February 8, 2013.
33. *Red Book Online*. Lubiprostone. Ann Arbor, Mich.: Truven Health Analytics. Available at: www.truvenhealth.com. Accessed February 8, 2013. ■